



(12) **EUROPEAN PATENT APPLICATION**  
published in accordance with Art. 158(3) EPC

(43) Date of publication:  
**10.08.2005 Bulletin 2005/32**

(51) Int Cl.<sup>7</sup>: **A61K 45/06, A61K 9/20,**  
**A61K 9/30, A61K 31/155,**  
**A61K 31/427, A61P 3/10**

(21) Application number: **03751344.7**

(22) Date of filing: **06.10.2003**

(86) International application number:  
**PCT/JP2003/012781**

(87) International publication number:  
**WO 2004/030700 (15.04.2004 Gazette 2004/16)**

(84) Designated Contracting States:  
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR**  
**HU IE IT LI LU MC NL PT RO SE SI SK TR**  
Designated Extension States:  
**AL LT LV MK**

(30) Priority: **07.10.2002 JP 2002294045**

(71) Applicant: **Takeda Pharmaceutical Company**  
**Limited**  
**Osaka 541-0045 (JP)**

(72) Inventors:  
• **KOIKE, Masahiko**  
**Takeda Pharmaceutical Company Ltd.**  
**Osaka-shi Osaka 532-8686 (JP)**

• **KOYAMA, Hiroyoshi**  
**Takeda Pharmaceut. Company Ltd.**  
**Osaka-shi Osaka 532-8686 (JP)**  
• **HAMAGUCHI, Naoru**  
**Takeda Pharmaceut. Company Ltd.**  
**Osaka-shi Osaka 532-8686 (JP)**

(74) Representative:  
**Rickard, Timothy Mark Adrian et al**  
**Takeda Euro IP Department,**  
**11-12 Charles II Street**  
**London SW1Y 4QU (GB)**

(54) **SOLID PREPARATION**

(57) The present invention provides a solid preparation containing an insulin sensitizer and an active ingredient (except insulin sensitizers), which is useful as a therapeutic drug for diabetes and the like, and which is superior in preparation characteristics such as con-

tent uniformity and dissolution property of the insulin sensitizer and the active ingredient (except insulin sensitizers), preparation hardness and the like.

**Description****Technical Field**

5 **[0001]** The present invention relates to a solid preparation comprising an insulin sensitizer and an active ingredient (except insulin sensitizers), which is useful as a therapeutic drug for diabetes and the like.

**Background Art**

10 **[0002]** There are the following reports on preparations containing an insulin sensitizer such as a thiazolidinedione and the like and an active ingredient (except insulin sensitizers).

- 1) A pharmaceutical agent containing an insulin sensitizer in combination with at least one member from an  $\alpha$ -glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthetase inhibitor, a fibrate compound, an LDL catabolism enhancer and an angiotensin converting enzyme inhibitor (EP749751A).
- 2) A pharmaceutical composition containing an insulin sensitizer, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier (WO98/57634, US2002/0004515A).
- 3) A pharmaceutical composition containing a thiazolidinedione, metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione is formulated upon the surface of metformin hydrochloride (WO01/35940).
- 4) A pharmaceutical composition containing a thiazolidinedione, metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione and metformin hydrochloride are respectively dispersed in pharmaceutically acceptable carriers of their own (WO01/35941).
- 25 5) A core formulation comprising (a) a first layer containing pioglitazone hydrochloride or a pharmaceutically acceptable salt thereof as an active ingredient, and (b) a core containing a biguanide as an active ingredient, wherein at least a portion of the core is enclosed by said first layer (WO01/82875).
- 6) a composition for treating diabetes, which contains an insulin sensitizer and an antidiabetic agent (USP6153632, WO02/04024).

**Disclosure of the Invention**

**[0003]** The present invention aims at providing a solid preparation comprising an insulin sensitizer and an active ingredient (except insulin sensitizers), which is useful as a therapeutic drug for diabetes and the like and which is superior in preparation characteristics such as content uniformity and dissolution property of the insulin sensitizer and the active ingredient (except insulin sensitizers), preparation hardness and the like.

**[0004]** The present inventors have found that a solid preparation superior in content uniformity of insulin sensitizer and preparation hardness can be obtained by, when producing a solid preparation containing an insulin sensitizer and an active ingredient (except insulin sensitizers), uniformly dispersing both components. The present inventors have further studied based on this finding and, as a result, completed the present invention.

**[0005]** That is, the present invention relates to

- 1) a solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, and a hardness of 100 to 400N;
- 2) the solid preparation of the aforementioned 1), wherein the active ingredient is a biguanide;
- 3) the solid preparation of the aforementioned 2), wherein the biguanide is metformin hydrochloride;
- 4) a solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) having a ratio of median size thereof to the median size of said insulin sensitizer of 0.5 to 15 are uniformly dispersed;
- 5) the solid preparation of the aforementioned 4), wherein the active ingredient is a biguanide;
- 6) the solid preparation of the aforementioned 5), wherein the biguanide is metformin hydrochloride;
- 7) a solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, and a coefficient of variation of the insulin sensitizer content of not more than 6%;
- 8) the solid preparation of the aforementioned 7), wherein the active ingredient is a biguanide;
- 9) the solid preparation of the aforementioned 8), wherein the biguanide is metformin hydrochloride;
- 10) a solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, which elutes out not less than 70% of the insulin sensitizer at 30 min after in a dissolution test according to a Paddle Method using a hydrochloric acid-potassium chloride buffer (pH 2.0) as a

test solution at 37°C, 50 rpm;

11) the solid preparation of the aforementioned 10), wherein the active ingredient is a biguanide;

12) the solid preparation of the aforementioned 11), wherein the biguanide is metformin hydrochloride;

13) a solid preparation having a phase wherein pioglitazone hydrochloride and metformin hydrochloride having a ratio of median size thereof to the median size of said pioglitazone hydrochloride of 0.5 to 15 are uniformly dispersed;

14) the solid preparation of the aforementioned 13), which is film-coated; and the like.

**[0006]** The insulin sensitizer to be used in the present invention may be any pharmaceutical agent as long as it restores damaged insulin receptor function and improves insulin resistance. As specific examples of the insulin sensitizer, the following compounds and salts thereof can be mentioned:

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (general name: pioglitazone);

5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (general name: rosiglitazone);

5-[[6-(2-fluorobenzyloxy)-2-naphthyl]methyl]-2,4-thiazolidinedione (general name: netoglitazone);

5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-[4-(trifluoromethyl)benzyl]benzamide (KRP-297);

4-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]isoxazolidine-3,5-dione (JTT-501); FK-614; Tesaglitazar (AZ-242); Ragaglitazar (NN-622);

BMS-298585; ONO-5816; CS-011; BM-13-1258; LM-4156; MBX-102; LY-519818; MX-6054; LY-510929; and (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid.

**[0007]** As the salt of the above-mentioned compound, pharmacologically acceptable salts such as salts with inorganic base, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like can be mentioned.

**[0008]** As preferable examples of the salts with inorganic base, for example, salts with alkali metals (e.g. sodium, potassium and the like), alkaline earth metals (e.g. calcium, magnesium and the like), aluminum, ammonium and the like can be mentioned.

**[0009]** As preferable examples of the salts with organic base, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like can be mentioned.

**[0010]** As preferable examples of the salts with inorganic acid, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like can be mentioned.

**[0011]** As preferable examples of the salts with organic acid, for example, salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

**[0012]** As preferable examples of the salts with basic amino acid, for example, salts with arginine, lysine, ornithine and the like can be mentioned, and as preferable examples of the salts with acidic amino acid, for example, salts with aspartic acid, glutamic acid and the like can be mentioned.

**[0013]** The insulin sensitizer is preferably pioglitazone hydrochloride, rosiglitazone maleate and the like, and particularly preferably pioglitazone hydrochloride.

**[0014]** In the present invention, two or more kinds of the insulin sensitizers may be used at an appropriate ratio.

**[0015]** The median size of the insulin sensitizer is preferably 1-100 µm, more preferably 1-70 µm. Particularly, when the insulin sensitizer is pioglitazone hydrochloride, the median size of pioglitazone hydrochloride is preferably 1-25 µm, more preferably 2-21 µm. Particularly, by the use of pioglitazone hydrochloride having a median size of 2 to 10 µm, a solid preparation superior in dissolution property of pioglitazone hydrochloride can be obtained.

**[0016]** The above-mentioned preferable median size is applied to an insulin sensitizer used as a starting material (including a pulverized product obtained by pulverizing, a mixed pulverized product obtained by pulverizing together with an excipient, and the like during the production process of a solid preparation) for producing the solid preparation of the present invention. In other words, the median size of an insulin sensitizer may have changed due to the coagulation of insulin sensitizer and the like, during the production process of the solid preparation of the present invention, or during the process of preserving the solid preparation after production.

**[0017]** In the present specification, by the median size is meant a particle size that divides crude particles from fine granules at 50% each in weight distribution or number distribution. The median size can be measured using, for example, a known measurement device such as a laser diffraction particle distribution apparatus (e.g., HELOS&RODOS (trade name, manufactured by SYMPATEC GmbH) and the like.

**[0018]** As the insulin sensitizer having a desired median size mentioned above, for example, a commercially available product can be used. In addition, the insulin sensitizer having a desired median size can be also produced by pulverizing an insulin sensitizer having a large median size together with an excipient such as microcrystalline cellulose and the

like as necessary. Here, the pulverization is performed according to a known method using, for example, a cutter mill, a hammer mill, a jet mill and the like.

[0019] In particular, when a solid preparation is produced using an insulin sensitizer having a weak binding force and a comparatively large median size, use of a large amount of additives such as a binder and the like, and the like may be designed to achieve sufficient preparation hardness. However, by making the median size of an insulin sensitizer smaller, a large amount of additives such as a binder and the like becomes unnecessary, which makes it possible to increase the drug content of a solid preparation.

[0020] As for the insulin sensitizer having a desired median size mentioned above, the dispersibility thereof is preferably such that "particles of not more than 0.1  $\mu\text{m}$  are contained at not more than 10% of the total amount, and particles of not less than 1000  $\mu\text{m}$  are contained at not more than 10% of the total amount".

[0021] As the active ingredient (except insulin sensitizers) to be used in the present invention, therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents, antiobesity agents, diuretics, antithrombotic agents and the like can be mentioned. These active ingredients may be a low-molecular-weight compound, a high-molecular-weight protein, polypeptide or antibody, a vaccine and the like. The active ingredient may be a mixture of two or more kinds of components at an appropriate ratio.

[0022] Examples of the therapeutic agents for diabetes include insulin preparations (e.g., animal insulin preparations extracted from the pancreas of bovine, swine; human insulin preparations synthesized by genetic engineering techniques using *Escherichia coli* or yeast; zinc insulin; protamine zinc insulin; fragments or derivatives of insulin (e.g., INS-1 etc.) and the like),  $\alpha$ -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate etc.), biguanide (e.g., phenformin, metformin, buformin, or a salt thereof (e.g., hydrochloride, fumarate, succinate) etc.), insulin secretagogues [sulfonylureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole etc.), repaglinide, nateglinide, mitiglinide or calcium salt hydrate thereof, GLP-1 etc.], dipeptidylpeptidase IV inhibitors (e.g., NVP-DPP-278, PT-100, NVP-DDP-728, LAF237, etc.),  $\beta$ 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ-40140 etc.), amylin agonists (e.g., pramlintide etc.), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists etc.) and SGLUT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 etc.).

[0023] Examples of the therapeutic agents for diabetic complications include aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat (SNK-860), CT-112 etc.), neurotrophic factors (e.g., NGF, NT-3, BDNF etc.), neurotrophin production-secretion promoters [e.g., neurotrophin production-secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-(3-(2-methylphenoxy)propyl)oxazole and the like)], PKC inhibitors (e.g., LY-333531 etc.), AGE inhibitors (e.g., ALT946, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT766), EXO-226 etc.), active oxygen scavengers (e.g., thiocetic acid etc.) and cerebral vasodilators (e.g., tiapride, mexiletine etc.).

[0024] Examples of the therapeutic agents for hyperlipidemia include HMG-CoA reductase inhibitors (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522, or their salts (e.g., sodium salts, calcium salts, etc.), etc.), fibrate compounds (e.g., bezafibrate, beclofibrate, binifibrate, ciprofibrate, ciprofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate etc.), squalene synthase inhibitors (e.g., compounds described in WO97/10224 (e.g., 1-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzooxazepin-3-yl]acetyl]piperidine-4-acetic acid, etc.), ACAT inhibitors (e.g., Avasimibe, Eflucimibe etc.), anion exchange resins (e.g., colestyramine etc.), probucol, nicotinic acid drugs (e.g., nicomol, niceritrol etc.), ethyl icosapentate, plant sterols (e.g., soysterol,  $\gamma$ -oryzanol etc.) and the like.

[0025] Examples of the antihypertensive agents include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril etc.), angiotensin II antagonists (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, tasosartan etc.), calcium antagonists (e.g., manidipine, nifedipine, nicardipine, amlodipine, efonidipine etc.), potassium channel openers (e.g., levromakalim, L-27152, AL 0671, NIP-121 etc.), clonidine and the like.

[0026] Examples of the antiobesity agents include antiobesity agents acting on the central nervous system (e.g., dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropylamine, clobenzorex etc.), pancreatic lipase inhibitors (e.g., orlistat etc.),  $\beta$ 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ-40140 etc.), peptidic anorexiant (e.g., leptin, CNTF (Ciliary Neurotrophic Factor) etc.), cholecystokinin agonists (e.g., linitript, FPL-15849 etc.) and the like.

[0027] Examples of the diuretics include xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine etc.), thiazide preparations (e.g., ethiazide, cyclopenthiiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzyhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide etc.), antialdosterone preparations (e.g., spironolactone, triamterene etc.), carbonate dehydratase inhibitors (e.g., acetazolamide etc.), chlorobenzenesulfonamide preparations (e.g., chlortalidone, mefruside, indapamide etc.), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like.

**[0028]** Examples of the antithrombotic agents include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium etc.), warfarin (e.g., warfarin potassium etc.), anti-thrombin drugs (e.g., aragatroban etc.), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase etc.), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride etc.) and the like.

**[0029]** The active ingredient (except insulin sensitizers) to be used in the present invention is preferably a therapeutic agent for diabetes, more preferably a biguanide and a sulfonylurea, particularly preferably metformin or a salt thereof (preferably metformin hydrochloride).

**[0030]** The median size of the active ingredient (except insulin sensitizers) is preferably 0.5 to 1000  $\mu\text{m}$ , more preferably 1 to 200  $\mu\text{m}$ . Particularly, when the active ingredient is a biguanide (preferably metformin hydrochloride), the median size of the biguanide (preferably metformin hydrochloride) is preferably 10 to 100  $\mu\text{m}$ , more preferably 10 to 80  $\mu\text{m}$ .

**[0031]** The above-mentioned preferable median size is applied to an active ingredient (except insulin sensitizers) used as a starting material (including a pulverized product obtained by pulverizing, a mixed pulverized product obtained by pulverizing together with an excipient, and the like, during the production process of a solid preparation) for producing the solid preparation of the present invention. In other words, the median size of an active ingredient may have changed due to the coagulation of the active ingredient and the like, during the production process of the solid preparation of the present invention, or during the process of preserving the solid preparation after production.

**[0032]** As the active ingredient (except insulin sensitizers) having a desired median size mentioned above, for example, a commercially available product can be used. In addition, the active ingredient having a desired median size can be also produced by pulverizing an active ingredient having a large median size. Here, the pulverization is performed according to a known method using, for example, a cutter mill, a hammer mill, a jet mill and the like.

**[0033]** In particular, when a solid preparation is produced using an active ingredient having a weak binding force and a comparatively large median size, use of a large amount of additives such as a binder and the like, and the like may be designed to achieve sufficient preparation hardness. However, by making the median size of an active ingredient smaller, a large amount of additives such as a binder and the like becomes unnecessary, which makes it possible to increase the drug content of the solid preparation.

**[0034]** As for the active ingredient (except insulin sensitizers) having a desired median size mentioned above, the dispersibility thereof is preferably such that "particles of not more than 0.1  $\mu\text{m}$  are contained at not more than 1% of the total amount, and particles of not less than 3000  $\mu\text{m}$  are contained at not more than 10% of the total amount".

**[0035]** The ratio of the median size of the aforementioned active ingredient (except insulin sensitizers) to the median size of the aforementioned insulin sensitizer is preferably 0.5 to 15, more preferably 0.5 to 10.

**[0036]** By employing such ratio of the median size, the insulin sensitizer and the active ingredient can be dispersed more uniformly.

**[0037]** The above-mentioned preferable ratio is applied to an insulin sensitizer and an active ingredient used as a starting material (including a pulverized product obtained by pulverizing, a mixed pulverized product obtained by pulverizing together with an excipient, and the like, during the production process of a solid preparation) for producing the solid preparation of the present invention. In other words, the above-mentioned preferable ratio may have changed during the production process of the solid preparation of the present invention, or during the process of preserving the solid preparation after production.

**[0038]** The most preferable combination of an insulin sensitizer and an active ingredient (except insulin sensitizers) in the solid preparation of the present invention is that of pioglitazone hydrochloride and metformin hydrochloride.

**[0039]** The solid preparation of the present invention has a phase (part) wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed.

**[0040]** That is, the solid preparation of the present invention may be a preparation wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed in the entirety of the preparation, or may be a preparation partially containing such preparation, such as a coated preparation obtained by coating a preparation wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed in the entirety of the preparation, and the like.

**[0041]** In the present invention, as a dosage form of a solid preparation, for example, tablet, capsule, granule, powder, troche and the like can be mentioned. The dosage form of a solid preparation is preferably tablet. Furthermore, the shape of the solid preparation may be any such as round, caplet, oblong and the like. When the weight of the solid preparation is large, the shapes of caplet and oblong are preferable from the aspect of easy administration.

**[0042]** The solid preparation of the present invention may contain an additive conventionally used for the technical field of formulation of preparations. As such additive, for example, excipient, disintegrant, binder, lubricant, coloring agent, pH adjusting agent, surfactant, stabilizer, acidulant, flavor, glidant and the like can be mentioned. These additives are used in the amounts conventionally employed in the technical field of formulation of preparations.

**[0043]** As the excipient, for example, starches such as cornstarch, potato starch, wheat starch, rice starch, partly pregelatinized starch, pregelatinized starch, porous starch and the like; sugars and sugar alcohols such as lactose,

fructose, glucose, mannitol, sorbitol and the like; anhydrous calcium phosphate, microcrystalline cellulose, precipitated calcium carbonate, calcium silicate and the like can be mentioned.

[0044] As the disintegrant, for example, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropyl cellulose, hydroxypropyl starch and the like are used. The amount of the disintegrant to be used is preferably 0.5-25 parts by weight, more preferably 1-15 parts by weight, per 100 parts by weight of the solid preparation.

[0045] As the binder, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, gum arabic powder and the like can be mentioned. The amount of the binder to be used is preferably 0.1-50 parts by weight, more preferably 0.5-40 parts by weight, per 100 parts by weight of the solid preparation. The binder is preferably hydroxypropyl cellulose or polyvinylpyrrolidone. Particularly, when the active ingredient to be used in the present invention is metformin hydrochloride, polyvinylpyrrolidone is preferable.

[0046] Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, sucrose esters of fatty acids, sodium stearyl fumarate and the like.

[0047] As the coloring agent, for example, food colors such as Food Yellow No. 5, Food Red No. 2, Food Blue No. 2 and the like, food lake colors, diiron trioxide and the like can be mentioned.

[0048] As the pH adjusting agent, citrate, phosphate, carbonate, tartrate, fumarate, acetate, amino acid salt and the like can be mentioned.

[0049] As the surfactant, sodium lauryl sulfate, polysorbate 80, polyoxyethylene (160) polyoxypropylene (30) glycol and the like can be mentioned.

[0050] As the stabilizer, for example, tocopherol, tetrasodium edetate, nicotinamide, cyclodextrins and the like can be mentioned.

[0051] As the acidulant, for example, ascorbic acid, citric acid, tartaric acid, malic acid and the like can be mentioned.

[0052] As the flavor, for example, menthol, peppermint oil, lemon oil, vanillin and the like can be mentioned.

[0053] As the glidant, for example, light silicic anhydride, hydrated silicon dioxide and the like can be mentioned. As used herein, light silicic anhydride may be any as long as it contains silicon dioxide hydrate ( $\text{SiO}_2 \cdot n\text{H}_2\text{O}$ ) ( $n$  is an integer) as the main component, and as concrete examples thereof, Sylsilia320 (trade name, Fuji Silysia Chemical Ltd.), AEROSIL200 (trade name, NIPPON AEROSIL CO., LTD.) and the like can be mentioned.

[0054] The above-mentioned additives may be used in a mixture of two or more kinds thereof at an appropriate ratio.

[0055] The insulin sensitizer content of the solid preparation of the present invention is, for example, 0.01-100 parts by weight, preferably 1-99 parts by weight, per 100 parts by weight of the solid preparation of the present invention.

[0056] Particularly, when the insulin sensitizer is pioglitazone hydrochloride, the pioglitazone hydrochloride content of the solid preparation of the present invention is, for example, preferably 0.01-15 parts by weight, more preferably 0.5-10 parts by weight, per 100 parts by weight of the solid preparation of the present invention.

[0057] The content of the active ingredient (except insulin sensitizers) in the solid preparation of the present invention is, for example, 0.1-100 parts by weight, preferably 1-99 parts by weight, per 100 parts by weight of the solid preparation of the present invention.

[0058] Particularly, when the active ingredient (except insulin sensitizers) is biguanide (preferably metformin hydrochloride), the biguanide (preferably metformin hydrochloride) content of the solid preparation of the present invention is, for example, preferably 5-98 parts by weight, more preferably 15-96 parts by weight, per 100 parts by weight of the solid preparation of the present invention.

[0059] The solid preparation of the present invention can be produced by, for example, uniformly mixing an insulin sensitizer and an active ingredient (except insulin sensitizers) with the aforementioned additives as necessary, or uniformly mixing after granulating, and then compression-molding.

[0060] Here, mixing is performed using, for example, a mixer such as a V-type mixer, a tumbler mixer and the like, and granulation is performed using, for example, a high speed mixer granulator, a fluid bed granulator-dryer and the like. For compression-molding, for example, punching is done generally at a pressure of 5-35 kN/cm<sup>2</sup> using a single punch tableting machine, a rotary tableting machine and the like.

[0061] For compression-molding using the aforementioned tableting machine, a tapered die is preferably used for preventing capping.

[0062] The solid preparation of the present invention is preferably produced by granulating an insulin sensitizer and an active ingredient (except insulin sensitizers) together with additives as necessary, such as excipient, glidant and the like, while spraying a solvent (e.g., water, ethanol) containing a binder (preferably polyvinylpyrrolidone when the active ingredient is metformin hydrochloride) dispersed or dissolved therein, drying the obtained granules, mixing the granules with additives such as excipient, disintegrant, lubricant and the like and then compression-molding the mixture.

[0063] A coated preparation can be also produced by coating a molded product obtained by compression-molding as mentioned above with a coating base.

[0064] As the coating base here, for example, a sugar coating base, a water-soluble film coating base, an enteric film coating base, a sustained-release film coating base and the like can be mentioned.

**[0065]** As the sugar coating base, sucrose is used, and one or more kinds selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be further used in combination.

**[0066]** As the water-soluble film coating base, for example, cellulose polymers such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methylhydroxyethyl cellulose etc.; synthetic polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E (trade name), Rohm Pharma], polyvinylpyrrolidone etc.; polysaccharides such as pullulan etc.; and the like can be mentioned.

**[0067]** As the enteric film coating base, for example, cellulose polymers such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, cellulose acetate phthalate etc.; acrylic polymers such as methacrylic acid copolymer L [Eudragit L (trade name), Rohm Pharma], methacrylic acid copolymer LD [Eudragit L-30D55 (trade name), Rohm Pharma], methacrylic acid copolymer S [Eudragit S (trade name), Rohm Pharma] etc.; naturally occurring substances such as shellac etc.; and the like can be mentioned.

**[0068]** As the sustained-release film coating base, for example, cellulose polymers such as ethyl cellulose etc.; acrylic polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trade name), Rohm Pharma], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name), Rohm Pharma] etc.; and the like can be mentioned.

**[0069]** The aforementioned coating bases may be used after mixing with two or more kinds thereof at appropriately ratios. For coating, coating additives may be used.

**[0070]** As the coating additive, for example, light shielding agent and/or coloring agent such as titanium oxide, talc, diiron trioxide and the like; plasticizers such as polyethylene glycol, triethyl citrate, castor oil, polysorbates and the like; organic acids such as citric acid, tartaric acid, malic acid, ascorbic acid and the like; and the like can be mentioned.

**[0071]** The coating is performed according to known methods, for example, using a film coating equipment.

**[0072]** When a coated preparation is produced by coating the above-mentioned molded product, the proportion of the molded product is generally 70-99 parts by weight, preferably 90-98 parts by weight, per 100 parts by weight of the coated preparation.

**[0073]** In addition, a mark or a letter may be printed on the solid preparation of the present invention for identifiability, and a separating line may be made to facilitate division.

**[0074]** From the aspects of preparation strength and the like, the solid preparation of the present invention is preferably film coated.

**[0075]** The solid preparation of the present invention preferably has a hardness of 100 to 400N.

**[0076]** The solid preparation of the present invention preferably has a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers), which has a ratio of median size thereof to the median size of said insulin sensitizer of 0.5 to 15 (preferably 0.5 to 10), are uniformly dispersed.

**[0077]** The above-mentioned preferable ratio is applied to an insulin sensitizer and an active ingredient used as a starting material (including a pulverized product obtained by pulverizing, a mixed pulverized product obtained by pulverizing together with an excipient, and the like, during the production process of a solid preparation) for producing the solid preparation of the present invention. In other words, the above-mentioned preferable ratio may have changed during the production process of the solid preparation of the present invention, or during the process of preserving the solid preparation after production.

**[0078]** The solid preparation of the present invention preferably shows a coefficient of variation of the insulin sensitizer content of not more than 6%. The coefficient of variation is preferably not more than 4%.

**[0079]** As used herein, the "coefficient of variation of the insulin sensitizer content" is a percentage (%) obtained by calculating the average value and the standard deviation of insulin sensitizer contents of plural solid preparations and dividing the standard deviation by the average value. The insulin sensitizer content of the solid preparation can be measured by known methods (e.g., liquid chromatography).

**[0080]** The solid preparation of the present invention preferably elutes out not less than 70% of the insulin sensitizer at 30 min after in a dissolution test according to a Paddle Method using a hydrochloric acid-potassium chloride buffer (pH 2.0) as a test solution at 37°C, 50 rpm.

**[0081]** Here, the dissolution test is performed according to a method described in the Japanese Pharmacopoeia 14th Edition. In addition, the "hydrochloric acid-potassium chloride buffer (pH 2.0)" to be used as a test solution can be prepared according to a known method. The amount of the hydrochloric acid-potassium chloride buffer to be used as a test solution is generally 900 mL.

**[0082]** The solid preparation of the present invention can be administered orally or parenterally and safely to mammals (e.g., mouse, rat, rabbit, cat, dog, bovine, horse, monkey, human and the like).

**[0083]** The solid preparation of the present invention and each component (e.g., insulin sensitizer such as pioglitazone hydrochloride and the like) in the solid preparation are useful as an agent for the prophylaxis or treatment of, for example, diabetes (e.g., type-1 diabetes, type-2 diabetes, gestational diabetes etc.), hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-HDL-emia, postprandial hyperlipidemia etc.), impaired glucose tolerance [IGT (Impaired Glucose Tolerance)], diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroan-

giopathy, osteopenia, hyperosmolar diabetic coma, infectious disease (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection etc.), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder etc.), obesity, osteoporosis, cachexia (e.g., cancerous cachexia, tuberculous cachexia, diabetic cachexia, blood disease cachexia, endocrine disease cachexia, infectious disease cachexia or cachexia due to acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, kidney disease (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage kidney disease etc.), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular accident (e.g., cerebral infarction, cerebral apoplexy), insulin resistance syndrome, Syndrome X, Dysmetabolic syndrome, hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostate cancer, skin cancer etc.), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases [e.g., Alzheimer's disease, chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, remission of tumentia, neuralgia, pharyngolaryngitis, cystitis, hepatitis (inclusive of nonalcoholic steatohepatitis), pneumonia, pancreatitis, inflammatory bowel disease, ulcerative colitis, etc.], visceral obesity syndrome, arteriosclerosis (e.g., atherosclerosis etc.) and the like.

**[0084]** The solid preparation of the present invention and each component (e.g., insulin sensitizer such as pioglitazone hydrochloride and the like) in the solid preparation are useful for the secondary prevention of various diseases mentioned above (e.g., secondary prevention of cardiovascular event such as cardiac infarction etc.) and suppression of progression (e.g., suppression of progression of impaired glucose tolerance into diabetes, suppression of progression of arteriosclerosis in diabetic patients).

**[0085]** The dose of the solid preparation of the present invention only needs to be an effective amount of an insulin sensitizer and an active ingredient (except insulin sensitizers) contained in the solid preparation.

**[0086]** The effective dose of the insulin sensitizer is, for example, generally 0.01-500 mg/day, preferably 0.1-100 mg/day, for an adult (body weight 60 kg).

**[0087]** Particularly, the effective amount of pioglitazone hydrochloride is generally 7.5-60 mg/day, preferably 15-60 mg/day, for an adult (body weight 60 kg), when the insulin sensitizer is pioglitazone hydrochloride.

**[0088]** When the insulin sensitizer is rosiglitazone malate, the effective amount of rosiglitazone malate is generally 1-12 mg/day, preferably 2-8 mg/day, for an adult (body weight 60 kg).

**[0089]** The effective amount of the active ingredient (except insulin sensitizers) is, for example, generally 0.01-10000 mg/day, preferably 0.1-5000 mg/day, for an adult (body weight 60 kg).

**[0090]** Particularly, the effective amount of a biguanide (preferably metformin hydrochloride) is generally 125-2550 mg/day, preferably 250-2550 mg/day, for an adult (body weight 60 kg), when the active ingredient is the biguanide (preferably metformin hydrochloride).

**[0091]** The frequency of the administration of the solid preparation of the present invention to the aforementioned mammals per day is preferably 1 or 2 times a day, more preferably once a day. Particularly, the solid preparation of the present invention is preferably administered once to a mammal before breakfast.

**[0092]** The solid preparation of the present invention may be used in combination with one or more pharmaceutical agents selected from therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents, antiobesity agents, diuretics, antithrombotic agents and the like (hereinafter sometimes to be abbreviated as a concomitant drug). As such concomitant drugs, those exemplified above as the active ingredient can be used. The time of administration of the solid preparation of the present invention and that of the concomitant drug are not limited, and they may be administered simultaneously or in a staggered manner to the administration subject. In addition, the solid preparation of the present invention and the concomitant drug may be administered to an administration subject as a single preparation containing them.

**[0093]** The dose of the concomitant drug can be appropriately determined based on the dose employed clinically. In addition, the mixing ratio of the solid preparation of the present invention and the concomitant drug can be appropriately determined according to the administration subject, administration route, target disease, condition, combination, and the like. For example, when the administration subject is a human, the concomitant drug may be used in an amount of 0.01 to 100 parts by weight per 1 part by weight of the solid preparation of the present invention.

**[0094]** Use of the concomitant drug in this way provides superior effects such as 1) enhancing the action of the solid preparation of the present invention or the concomitant drug (synergistic effect on the action of the pharmaceutical agents), 2) reducing the dose of the solid preparation of the present invention or the concomitant drug (effect of reducing the dose of pharmaceutical agents as compared to a single drug administration), 3) reducing the secondary action of the solid preparation of the present invention or the concomitant drug, and the like.

**[0095]** The present invention further provides "a production method of a solid preparation having a phase (part) wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, which comprises fluidized bed-granulating the insulin sensitizer and the active ingredient (except insulin sensitizers) having a ratio of median size thereof to the median size of said insulin sensitizer of 0.5 to 15 (preferably 0.5 to 10).

**[0096]** Here, the fluidized bed granulating is performed according to a method known *per se*, for example, using a



fluidized granulating dryer and the like. Where necessary, additives such as an excipient, a glidant, a binder and the like may be added during or before fluidized bed granulating. Alternatively, the granules obtained by fluidized bed granulating may be mixed with additives such as an excipient, a disintegrant, a lubricant and the like as necessary, and compression-molded, and the obtained molded product may be further coated with a coating base.

[0097] As used herein, as the additive and coating base, those similar to the aforementioned can be used. In addition, the compression-molding and coating are performed in the same manner as the above.

[0098] The production method of the present invention is useful for the production of a solid preparation containing a highly water-soluble active ingredient (e.g., metformin hydrochloride) as a convenient production method of a solid preparation superior in preparation characteristics such as content uniformity and dissolution property of the active ingredient and an insulin sensitizer, preparation hardness and the like.

[0099] The present invention is explained in detail in the following by referring to Examples, Reference Examples, Comparative Example and Experimental Examples, which are not to be construed as limitative.

[0100] In the following Examples and Comparative Example, the median size was measured by Helos & Rodos (trade name, manufactured by Sympatec). In the Examples, moreover, as various additives such as magnesium stearate and the like, the Japanese Pharmacopoeia 14th Edition compatible products were used.

#### Example 1

[0101] Metformin hydrochloride (median size: 29  $\mu\text{m}$ , 267.6 g), pioglitazone hydrochloride (median size: 13  $\mu\text{m}$ , 8.7 g) and cornstarch (4.2 g) were placed in a fluidized granulating dryer (manufactured by POWREX CORPORATION, LAB-1), granulated while spraying purified water (195 g) containing polyvinylpyrrolidone (19.5 g) and dried to give granules.

[0102] Microcrystalline cellulose (18.87 g), croscarmellose sodium (16.85 g) and magnesium stearate (1.35 g) were added to and mixed with the obtained granules.

[0103] The obtained powder mixture was tableted using a tableting machine (manufactured by Kikusui Seisakusho, Ltd., Correct12HUK) (tablet size: long diameter 13.5 mm x short diameter 8.5 mm, compression pressure: 9.6 kN/cm<sup>2</sup>) to give tablets weighing 630 mg per tablet.

#### Example 2

[0104] Metformin hydrochloride (median size: 29  $\mu\text{m}$ , 2283.1 g), pioglitazone hydrochloride (median size: 13  $\mu\text{m}$ , 75.5 g), Sylsias320 (trade name, Fuji Silysia Chemical Ltd., 1.4 g), microcrystalline cellulose (85.7 g) were placed in a fluidized granulating dryer (manufactured by POWREX CORPORATION, FD-3SN), granulated while spraying purified water (1507 g) containing polyvinylpyrrolidone (150.7 g) and dried to give granules.

[0105] Microcrystalline cellulose (170 g), croscarmellose sodium (137.8 g) and magnesium stearate (9.1 g) were added to and mixed with the obtained granules.

[0106] The obtained powder mixture was tableted using a tableting machine (manufactured by Kikusui Seisakusho Ltd., Correct12HUK) (tablet size: long diameter 13.5 mm x short diameter 8.5 mm, compression pressure: 9.6 kN/cm<sup>2</sup>) to give tablets weighing 638 mg per tablet.

[0107] The obtained tablets (1200 g) were cast in a film coating apparatus (Hicoater 30, manufactured by POWREX CORPORATION), and coating was performed by spraying a coating solution at an entrance temperature of 80°C and at 2.0 g/min to give film-coated tablets weighing 657 mg per tablet. As the coating solution, a dispersion of hydroxypropylmethyl cellulose (22.0 g), polyethylene glycol 6000 (4.2 g), titanium oxide (4.2 g) and talc (4.2 g) in purified water (446 g) was used.

#### Example 3

[0108] Metformin hydrochloride (median size: 29  $\mu\text{m}$ , 2318.2 g), pioglitazone hydrochloride (median size: 13  $\mu\text{m}$ , 45.1 g), Sylsias320 (trade name, Fuji Silysia Chemical Ltd., 1.4 g) and microcrystalline cellulose (86.4 g) were placed in a fluidized granulating dryer (manufactured by POWREX CORPORATION, FD-3SN), granulated while spraying purified water (1500 g) containing polyvinylpyrrolidone (150 g) and dried to give granules.

[0109] Microcrystalline cellulose (170 g), croscarmellose sodium (138.2 g) and magnesium stearate (9.0 g) were added to and mixed with the obtained granules.

[0110] The obtained powder mixture was tableted using a tableting machine (manufactured by Kikusui Seisakusho Ltd., Correct12HUK) (tablet size: long diameter 17.5 mm x short diameter 9.5 mm, compression pressure: 11 kN/cm<sup>2</sup>) to give tablets weighing 1070 mg per tablet.

[0111] The obtained tablets (1200 g) were cast in a film coating apparatus (Hicoater 30, manufactured by POWREX CORPORATION), and coating was performed by spraying a coating solution at an entrance temperature of 80°C and

at 2.0 g/min to give film-coated tablets weighing 1100 mg per tablet. As the coating solution, a dispersion of hydroxypropylmethyl cellulose (20.7 g), polyethylene glycol 6000 (4.0 g), titanium oxide (4.0 g) and talc (4.0 g) in purified water (327 g) was used.

#### 5 Example 4

[0112] Metformin hydrochloride (median size: 29  $\mu$ m, 2325.6 g), pioglitazone hydrochloride (median size: 13  $\mu$ m, 38.4 g), Sylysia320 (trade name, Fuji Silysia Chemical Ltd., 1.4 g) and microcrystalline cellulose (88.1 g) were placed in a fluidized granulating dryer (manufactured by POWREX CORPORATION, FD-3SN), granulated while spraying purified water (1491 g) containing polyvinylpyrrolidone (149.1 g) and dried to give granules.

[0113] Microcrystalline cellulose (170 g), croscarmellose sodium (137.1 g) and magnesium stearate (8.8 g) were added to and mixed with the obtained granules.

[0114] The obtained powder mixture was tableted using a tableting machine (manufactured by Kikusui Seisakusho Ltd., Correct12HUK) (tablet size: long diameter 20.0 mm x short diameter 10.0 mm, compression pressure: 11 kN/cm<sup>2</sup>) to give tablets weighing 1255 mg per tablet.

[0115] The obtained tablets (1200 g) were cast in a film coating apparatus (Hicoater 30, manufactured by POWREX CORPORATION), and coating was performed by spraying a coating solution at an entrance temperature of 80°C and at 2.0 g/min to give film-coated tablets weighing 1290 mg per tablet. As the coating solution, a dispersion of hydroxypropylmethyl cellulose (20.8 g), polyethylene glycol 6000 (3.9 g), titanium oxide (3.9 g) and talc (3.9 g) in purified water (325 g) was used.

#### Example 5

[0116] Pioglitazone hydrochloride (median size: 13  $\mu$ m) (10000 g) and microcrystalline cellulose (2500 g) were cast into a mixer (POWREX CORPORATION, vertical granulator) and mixed by stirring. The obtained mixture was pulverized in a jet mill pulverizer (NPK Co., Ltd., 100SP) to give a pulverized product (median size 3.6  $\mu$ m) of a pioglitazone hydrochloride/microcrystalline cellulose mixture.

[0117] Metformin hydrochloride (median size: 29  $\mu$ m, 4250 g), a pulverized product (median size 3.6  $\mu$ m, 103.3 g) of a pioglitazone hydrochloride/microcrystalline cellulose mixture and microcrystalline cellulose (131.9 g) were cast in a fluidized granulating dryer (POWREX CORPORATION, FD-5S), granulated while spraying purified water (1375 g) containing polyvinylpyrrolidone (275 g), and dried to give granules.

[0118] Microcrystalline cellulose (320 g), croscarmellose sodium (253.4 g) and magnesium stearate (16.5 g) were added to and mixed with the obtained granules.

[0119] The obtained powder mixture was tableted using a tableting machine (manufactured by Kikusui Seisakusho Ltd., Correct12HUK) (tablet size: long diameter 17.5 mm x short diameter 9.5 mm, compression pressure: 20 kN/punch) equipped with a tapered die to give tablets weighing 1070 mg per tablet.

[0120] The obtained tablets (3600 g) were cast in a film coating apparatus (DRIACOATER500, manufactured by POWREX CORPORATION) and a coating solution was sprayed at an entrance temperature of 80°C at 15.0 g/min to give film-coated tablets weighing 1100 mg per tablet. As the coating solution, a dispersion of hydroxypropylmethyl cellulose (63.8 g), polyethylene glycol 6000 (12.3 g), titanium oxide (12.3 g) and talc (12.3 g) in purified water (1000 g) was used.

#### Example 6

[0121] Pioglitazone hydrochloride (median size: 13  $\mu$ m, 10000 g) and microcrystalline cellulose (2500 g) were cast into a mixer (POWREX CORPORATION, vertical granulator) and mixed by stirring. The obtained mixture was pulverized in a jet mill pulverizer (NPK Co., Ltd., 100SP) to give a pulverized product (median size 3.6  $\mu$ m) of a pioglitazone hydrochloride/microcrystalline cellulose mixture.

[0122] Metformin hydrochloride (median size: 29  $\mu$ m, 4500 g), a pulverized product (median size 3.6  $\mu$ m, 185.9 g) of a pioglitazone hydrochloride/microcrystalline cellulose mixture and microcrystalline cellulose (127.5 g) were cast in a fluidized granulating dryer (POWREX CORPORATION, FD-5S), granulated while spraying purified water (1485 g) containing polyvinylpyrrolidone (297 g), and dried to give granules.

[0123] Microcrystalline cellulose (342 g), croscarmellose sodium (271.5 g) and magnesium stearate (18 g) were added to and mixed with the obtained granules.

[0124] The obtained powder mixture was tableted using a tableting machine (manufactured by Kikusui Seisakusho Ltd., Correct12HUK) (tablet size: long diameter 13.5 mm x short diameter 8.5 mm, compression pressure: 15 kN/punch) equipped with a tapered die to give tablets weighing 638 mg per tablet.

[0125] The obtained tablets (3600 g) were cast in a film coating apparatus (DRIACOATER500, manufactured by

POWREX CORPORATION) and a coating solution was sprayed at an entrance temperature of 80°C at 15.0 g/min to give film-coated tablets weighing 657 mg per tablet. As the coating solution, a dispersion of hydroxypropylmethyl cellulose (67.4 g), polyethylene glycol 6000 (13 g), titanium oxide (13 g) and talc (13 g) in purified water (1064 g) was used.

## Reference Example 1

[Production of coating agent]

**[0126]** Hydroxypropylmethyl cellulose 2910 (TC-5) (350.4 g) and polyethylene glycol 6000 (72 g) were dissolved in purified water (4320 g). Titanium oxide (48 g) and yellow diiron trioxide (9.6 g) were dispersed in the obtained solution to give a coating agent.

[Production of naked tablet]

**[0127]** (E)-4-[4-(5-Methyl-2-phenyl-4-oxazolymethoxy)benzyloxyimino]-4-phenylbutyric acid (hereinafter to be abbreviated as Compound A, 1184 g), lactose (1991 g), cornstarch (366.3 g) and croscarmellose sodium (233.9 g) were placed in a fluidized bed granulator dryer (manufactured by POWREX CORPORATION), preheated, mixed and granulated while spraying an aqueous solution (2591 g) containing hydroxypropyl cellulose (142.5 g). The obtained granule powder (3696 g) was passed through a power mill (manufactured by Showa Chemical Machinery Engineering) to give a sized powder. The obtained sized powder (3485 g), cornstarch (127.1 g) and magnesium stearate (18.15 g) were mixed in a tumbler mixer (manufactured by Showa chemical machinery engineering) and the obtained mixed powder was tableted by a tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give naked tablets.

[Production of film-coated tablet]

**[0128]** The aforementioned coating agent was sprayed on the obtained 24000 naked tablets in a film coating machine (manufactured by POWREX CORPORATION) to give film-coated tablets (24000 tablets) containing 32.0 mg of Compound A per tablet and having the following formulation.

Tablet formulation (composition per tablet):		
(naked tablet)		
1)	Compound A	32.0 mg
2)	lactose	53.8 mg
3)	cornstarch	13.75 mg
4)	croscarmellose sodium	6.05 mg
5)	hydroxypropyl cellulose	3.85 mg
6)	magnesium stearate	0.55 mg
	total	110.0 mg
(film components)		
7)	hydroxypropylmethyl cellulose 2910	2.92 mg
8)	polyethylene glycol 6000	0.6 mg
9)	titanium oxide	0.4 mg
10)	yellow diiron trioxide	0.08 mg
	total	114.0 mg

## Reference Example 2

[Production of coating agent]

**[0129]** Hydroxypropylmethyl cellulose 2910 (TC-5) (101.9 g) and polyethylene glycol 6000 (20.4 g) were dissolved in purified water (1224 g). Titanium oxide (13.6 g) and yellow diiron trioxide (0.136 g) were dispersed in the obtained solution to give a coating agent.

[Production of naked tablet]

[0130] In the same manner as in Reference Example 1, a mixed powder was prepared and the obtained mixed powder was tableted by a tableting machine (Kikusui Seisakusho Ltd.) to give naked tablets.

[Production of film-coated tablet]

[0131] The aforementioned coating agent was sprayed on the obtained 600 naked tablets in a film coating machine (manufactured by Freund Corporation) to give film-coated tablets (600 tablets) containing 48.0 mg of Compound A per tablet and having the following formulation.

Tablet formulation (composition per tablet):		
(naked tablet)		
1)	Compound A	48.0 mg
2)	lactose	80.7 mg
3)	cornstarch	20.625 mg
4)	croscarmellose sodium	9.075 mg
5)	hydroxypropyl cellulose	5.775 mg
6)	magnesium stearate	0.825 mg
	total	165.0 mg
(film components)		
7)	hydroxypropylmethyl cellulose 2910	4.494 mg
8)	polyethylene glycol 6000	0.9 mg
9)	titanium oxide	0.6 mg
10)	yellow diiron trioxide	0.006 mg
	total	171.0 mg

### Reference Example 3

[Production of coating agent]

[0132] Hydroxypropylmethyl cellulose 2910 (TC-5) (101.2 g) and polyethylene glycol 6000 (20.4 g) were dissolved in purified water (1224 g). Titanium oxide (13.6 g) and yellow diiron trioxide (0.816 g) were dispersed in the obtained solution to give a coating agent.

[Production of naked tablet]

[0133] In the same manner as in Reference Example 1, a mixed powder was prepared and the obtained mixed powder was tableted by a tableting machine (Kikusui Seisakusho Ltd.) to give naked tablets.

[Production of film-coated tablet]

[0134] The aforementioned coating agent was sprayed on the obtained 320 naked tablets in a film coating machine (manufactured by Freund Corporation) to give film-coated tablets (320 tablets) containing 64.0 mg of Compound A per tablet and having the following formulation.

(naked tablet)		
1)	Compound A	64.0 mg
2)	lactose	107.6 mg
3)	cornstarch	27.5 mg
4)	croscarmellose sodium	12.1 mg
5)	hydroxypropyl cellulose	7.7 mg

# EP 1 561 472 A1

(continued)

(naked tablet)		
6)	magnesium stearate	1.1 mg
	total	220.0 mg
(film components)		
7)	hydroxypropylmethyl cellulose 2910	5.952 mg
8)	polyethylene glycol 6000	1.2 mg
9)	titanium oxide	0.8 mg
10)	yellow diiron trioxide	0.048 mg
	total	228.0 mg

## Reference Example 4

[Production of coating agent]

[0135] Hydroxypropylmethyl cellulose 2910 (TC-5) (298.8 g) and polyethylene glycol 6000 (60 g) were dissolved in purified water (3600 g). Titanium oxide (40 g) and yellow diiron trioxide (1.2 g) were dispersed in the obtained solution to give a coating agent.

[Production of naked tablet]

[0136] Compound A (1032 g), lactose (2657 g), cornstarch (425.7 g) and croscarmellose sodium (260.2 g) were placed in a fluidized bed granulator dryer (manufactured by POWREX CORPORATION), preheated, mixed and granulated while spraying an aqueous solution (2760 g) containing hydroxypropyl cellulose (165.6 g). The obtained granule powder (4277 g) was passed through a power mill (manufactured by Showa Chemical Machinery Engineering) to give a sized powder. The obtained sized powder (3696 g), cornstarch (134.8 g) and magnesium stearate (19.25 g) were mixed in a tumbler mixer (manufactured by Showa Chemical Machinery Engineering) and the obtained mixed powder was tableted by a tableting machine (Kikusui Seisakusho Ltd.) to give naked tablets.

[Production of film-coated tablet]

[0137] The aforementioned coating agent was sprayed on the obtained 27000 naked tablets in a film coating machine (manufactured by POWREX CORPORATION) to give film-coated tablets (27000 tablets) containing 24.0 mg of Compound A per tablet and having the following formulation.

Tablet formulation (composition per tablet):		
(naked tablet)		
1)	Compound A	24.0 mg
2)	lactose	61.8 mg
3)	cornstarch	13.75 mg
4)	croscarmellose sodium	6.05 mg
5)	hydroxypropyl cellulose	3.85 mg
6)	magnesium stearate	0.55 mg
	total	110.0 mg
(film components)		
7)	hydroxypropylmethyl cellulose 2910	2.988 mg
8)	polyethylene glycol 6000	0.6 mg
9)	titanium oxide	0.4 mg
10)	yellow diiron trioxide	0.012 mg
	total	114.0 mg

**Comparative Example 1**

[0138] In the same manner as in Example 1 except that metformin hydrochloride (median size: 29  $\mu\text{m}$ ) was replaced by metformin hydrochloride (median size: 238  $\mu\text{m}$ ), tablets were obtained.

**Experimental Example 1**

[0139] The tablets obtained in the aforementioned Examples and Comparative Example were evaluated for content uniformity of these drugs by determining the coefficient of variation (%) of pioglitazone hydrochloride and metformin hydrochloride.

[0140] To be specific, the contents of pioglitazone hydrochloride and metformin hydrochloride in the tablets were measured by liquid chromatography, the average value and standard deviation of 3 tablets were determined, after which the standard deviation was divided by the average value and the percentage thereof was calculated. The results are shown in Table 1.

[Table 1]

Coefficient of variation (%) of pioglitazone hydrochloride and metformin hydrochloride		
	pioglitazone hydrochloride	metformin hydrochloride
Example 1	3.5	0.8
Example 2	0.5	0.3
Example 3	1.1	0.7
Example 5	1.0	0.5
Example 6	0.6	0.5
Comparative Example 1	7.6	1.2

[0141] As shown in Table 1, the coefficient of variation of pioglitazone hydrochloride and metformin hydrochloride in the solid preparation of the present invention was small. In other words, the solid preparation of the present invention showed superior drug content uniformity.

**Experimental Example 2**

[0142] The tablets obtained in the aforementioned Examples and Comparative Example were measured for the tablet hardness in the long diameter direction using a tablet hardness meter (manufactured by Toyama Sangyo Co. Ltd.). The results are expressed in an average of 3 tablets. The results are shown in Table 2.

[Table 2]

Tablet hardness (N)	
	Tablet hardness (N)
Example 1	181
Example 2	210
Example 3	250
Example 5	223
Example 6	289
Comparative Example 1	80

[0143] As shown in Table 2, the solid preparation of the present invention showed superior tablet hardness.

**Experimental Example 3**

[0144] The tablets obtained in the aforementioned Examples were evaluated for the dissolution property of pioglitazone hydrochloride by the Paddle Method (50 rpm) using a hydrochloric acid-potassium chloride buffer (900 mL, 37°C,

pH 2.0). The results are shown in Table 3.

[Table 3]

Dissolution rate (%) of pioglitazone hydrochloride				
time	15 min	30 min	45 min	60 min
Example 2	85.6	95.8	98.5	99.5
Example 3	83.1	94.1	97.7	98.6
Example 5	93.0	100.7	-	-
Example 6	89.0	100.0	-	-

[0145] As shown in Table 3, the solid preparation of the present invention showed superior dissolution property of pioglitazone hydrochloride.

#### Industrially Applicability

[0146] The solid preparation of the present invention is useful as a therapeutic drug for diabetes and the like and is superior in preparation characteristics such as content uniformity and dissolution property of an insulin sensitizer and an active ingredient (except insulin sensitizers), preparation hardness and the like.

[0147] Moreover, the solid preparation of the present invention can be easily produced by a convenient method.

#### Claims

1. A solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, and a hardness of 100 to 400N.
2. The solid preparation of claim 1, wherein the active ingredient is a biguanide.
3. The solid preparation of claim 2, wherein the biguanide is metformin hydrochloride.
4. A solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) having a ratio of median size thereof to the median size of said insulin sensitizer of 0.5 to 15 are uniformly dispersed.
5. The solid preparation of claim 4, wherein the active ingredient is a biguanide.
6. The solid preparation of claim 5, wherein the biguanide is metformin hydrochloride.
7. A solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, and a coefficient of variation of the insulin sensitizer content of not more than 6%.
8. The solid preparation of claim 7, wherein the active ingredient is a biguanide.
9. The solid preparation of claim 8, wherein the biguanide is metformin hydrochloride.
10. A solid preparation having a phase wherein an insulin sensitizer and an active ingredient (except insulin sensitizers) are uniformly dispersed, which elutes out not less than 70% of the insulin sensitizer at 30 min after in a dissolution test according to a Paddle Method using a hydrochloric acid-potassium chloride buffer (pH 2.0) as a test solution at 37°C, 50 rpm.
11. The solid preparation of claim 10, wherein the active ingredient is a biguanide.
12. The solid preparation of claim 11, wherein the biguanide is metformin hydrochloride.
13. A solid preparation having a phase wherein pioglitazone hydrochloride and metformin hydrochloride having a ratio of median size thereof to the median size of said pioglitazone hydrochloride of 0.5 to 15 are uniformly dispersed.

**14.** The solid preparation of claim 13, which is film-coated.

5

10

15

20

25

30

35

40

45

50

55



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/12781

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int.Cl <sup>7</sup> A61K45/06, 9/20, 9/30, 31/155, 31/427, A61P3/10											
According to International Patent Classification (IPC) or to both national classification and IPC											
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int.Cl <sup>7</sup> A61K9/20-9/46, 31/155, 31/427, 45/00-45/08											
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched											
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS (STN), MEDLINE (STN), WPI (DIALOG)											
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y A</td> <td>WO 01/35941 A2 (SMITHKLINE BEECHAM P.L.C.), 25 May, 2001 (25.05.01), See especially, pages 14, 15 &amp; AU 200114040 A &amp; BR 200015605 A &amp; NO 200202334 A &amp; EP 1231918 A2 &amp; SK 200200679 A3 &amp; CZ 200201679 A3 &amp; ZA 200203865 A &amp; HU 200204122 A2 &amp; CN 1414852 A &amp; JP 2003-514012 A &amp; KR 2003019300 A &amp; NZ 518946 A</td> <td>1-3, 7-12 4-6, 13, 14</td> </tr> <tr> <td>Y</td> <td>Written and edited by Sadashi OKANO, "Shin-Yakuzaigaku Soron (Kaitei Dai 3 Han)", Nankodo Co., Ltd., 10 April, 1987 (10.04.87), pages 155 to 160; particularly, page 155, lower part; page 157, lower part; page 159, lower part</td> <td>1-3, 7-12</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y A	WO 01/35941 A2 (SMITHKLINE BEECHAM P.L.C.), 25 May, 2001 (25.05.01), See especially, pages 14, 15 & AU 200114040 A & BR 200015605 A & NO 200202334 A & EP 1231918 A2 & SK 200200679 A3 & CZ 200201679 A3 & ZA 200203865 A & HU 200204122 A2 & CN 1414852 A & JP 2003-514012 A & KR 2003019300 A & NZ 518946 A	1-3, 7-12 4-6, 13, 14	Y	Written and edited by Sadashi OKANO, "Shin-Yakuzaigaku Soron (Kaitei Dai 3 Han)", Nankodo Co., Ltd., 10 April, 1987 (10.04.87), pages 155 to 160; particularly, page 155, lower part; page 157, lower part; page 159, lower part	1-3, 7-12
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.									
Y A	WO 01/35941 A2 (SMITHKLINE BEECHAM P.L.C.), 25 May, 2001 (25.05.01), See especially, pages 14, 15 & AU 200114040 A & BR 200015605 A & NO 200202334 A & EP 1231918 A2 & SK 200200679 A3 & CZ 200201679 A3 & ZA 200203865 A & HU 200204122 A2 & CN 1414852 A & JP 2003-514012 A & KR 2003019300 A & NZ 518946 A	1-3, 7-12 4-6, 13, 14									
Y	Written and edited by Sadashi OKANO, "Shin-Yakuzaigaku Soron (Kaitei Dai 3 Han)", Nankodo Co., Ltd., 10 April, 1987 (10.04.87), pages 155 to 160; particularly, page 155, lower part; page 157, lower part; page 159, lower part	1-3, 7-12									
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.											
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family											
Date of the actual completion of the international search 16 January, 2004 (16.01.04)		Date of mailing of the international search report 10 February, 2004 (10.02.04)									
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer									
Facsimile No.		Telephone No.									

Form PCT/ISA/210 (second sheet) (July 1998)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/12781

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/30400 A1 (Takeda Chemical Industries, Ltd.), 18 April, 2002 (18.04.02), Particularly, page 25, lines 15 to 16 & AU 200194192 A & JP 2002-179558 A & EP 1329217 A1	1-3
A	WO 01/35940 A2 (SMITHKLINE BEECHAM P.L.C.), 25 May, 2001 (25.05.01), & AU 200114035 A & EP 1231917 A2 & JP 2003-514011 A	1-14
A	SUZUKI, Masami et al., Effects of combined pioglitazone and metformin on diabetes and obesity in Wistar fatty rats, Clinical and Experimental Pharmacology and Physiology, April 2002, Vol.29, No.4, pages 269 to 274	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/12781

**Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**This International Searching Authority found multiple inventions in this international application, as follows:  
(See extra sheet.)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest** ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/12781

Continuation of Box No. II of continuation of first sheet(1)

In claims, the matter common to (1) the inventions as set forth in claims 1 to 3; (2) the inventions as set forth in claims 4 to 6, 13 and 14; (3) the inventions as set forth in claims 7 to 9; and (4) the inventions as set forth in claims 10 to 12 resides in "improvement in uniformity in drug ingredient contents and preparation characteristics of a solid preparation containing an insulin resistance improving drug and an active ingredient (other than the insulin resistance improving drug)". However, "a solid preparation containing an insulin resistance improving drug and an active ingredient (other than the insulin resistance improving drug)" had been already publicly known before the filing of this international application (see, for example, WO 01/35941 A2 (SMITHKLINE BEECHAM P.L.C.) 2001.05.25) and improvement in uniformity in drug ingredient contents and solid characteristics is a problem which should be taken into consideration by those skilled in the art and was already well known at the filing of this international application. Thus, "improvement in uniformity of drug ingredient contents and preparation characteristics in a solid preparation containing an insulin resistance improving drug and an active ingredient (other than the insulin resistance improving drug)" cannot be regarded as "a special technical feature". That is, there is no "special technical feature" common to the invention groups (1) to (4) as described above.

Such being the case, the present claims have 4 groups of inventions (1) to (4) as described above which are different from each other.

## &lt;Subject of search&gt;

In claims, "an insulin resistance improving drug" and "an active ingredient" are presented as drug ingredients of the solid preparation. Since "an insulin resistance improving drug" and "an active ingredient" involve substances having various physical and chemical properties and the problem to be solved by the invention of the present international application closely relates to "improvement in uniformity in drug ingredient contents and preparation characteristics", i.e., the physical and chemical properties of the chemical ingredients, only parts of these ingredients are disclosed in the meaning within PCT Article 5 and sufficiently supported in the meaning within PCT Article 6.

Such being the case, the search was made on "pioglitazone and its salt" as the insulin resistance improving drug and "metformin and its salt" as the active ingredient.